

EXHIBIT 1
10/531,330

Claimed diseases	References showing the evidence and the corresponding recitations
<p>Chronic heart failure, Angina, Cardiac infarction</p>	<p>Nature, Vol. 407, No. 6806, 2000, pp. 870-876 "Large-conductance calcium-activated potassium channels (BK channels) are pivotal in the regulation of arterial tone, where they facilitate a negative feedback mechanism which opposes vasoconstriction" (p. 870, L. 7)</p> <p>The Journal of Pharmacology and Experimental Therapeutics, Vol. 284, No. 3, 1998, pp. 838-846 "This study investigated nitroglycerin (NTG) relaxations in isolated dog coronary artery in comparison with other vascular preparations. Under maximal PNU-46619 precontraction, the coronary artery was significantly more sensitive to NTG than mesenteric artery, mesenteric vein and saphenous vein. In the coronary artery, NTG (1-100 nM) produced relaxations with EC50 5 9.4 nM. In KCl-contracted arteries (20-80 mM KCl), relaxation by NTG was progressively reduced. <u>Relaxation responses to NTG also were inhibited significantly by potent calcium-activated K1 (BK) channel blockers, charybdotoxin (100 nM) and iberiotoxin (200 nM), but not by KATP blockers such as PNU-37883A (10 mM) or PNU-99963 (100 nM).</u>" (Abstract)</p> <p>"Finally, comparative studies with NTG, NO and ACh show that BK channel blockers produce significant inhibition of relaxations by all three agents in the coronary artery. Thus, <u>BK channel activation apparently is a key mechanism for coronary artery relaxation</u> by cyclic GMP-mediated vasodilators such as, NTG, ACh and NO." (p. 845, right col. L. 6)</p>
<p>Hypertension</p>	<p>Current Pharmaceutical Design, Vol. 2, No. 4, 1996, pp.413-428 P.425, right column, Chapter of Hypertension</p>
<p>Cerebral infarction, Subarachnoid Hemorrhage, Cerebral vasospasm, Cerebral hypoxia, Cerebral apoplexy, Cerebral ischemia, Traumatic encephalopathy</p>	<p>Journal of Cerebral Blood Flow and Metabolism, 21(4), 2001, pp.396-403 "Large-conductance, calcium-activated potassium (maxi-K) channels regulate neurotransmitter release and neuronal excitability, and openers of these channels have been shown to be neuroprotective in models of cerebral ischemia" (Abstract, L.1) "These beneficial results, in a clinically relevant model of brain injury, are suggestive of the potential use of this maxi-K channel opener as a therapeutic agent for the treatment of TBI, and future studies should attempt to assess the therapeutic window for this compound." (P.401, right col. L.1)</p>

	<p>US 6,184,231 B1</p> <p>"Selected compounds have been evaluated in the focal stroke model involving permanent MCAO in the spontaneously hypertensive rat. This procedure results in a reliably large neocortical infarct volume that is measured by means of vital dye exclusion in serial slices through the brain 24 hours after MCAO. In the present test, compounds were administered using an intravenous route of administration at 2 hours after occlusion. For example, in this model, the compound of Example 21 reduced the cortical infarct volume by about 25% when administered (0.003 mg/kg) as a single bolus 2 hours after middle cerebral artery occlusion as compared to vehicle-treated (2% DMSO, 98% propylene glycol) control." (column 23 L. 23)</p>
Asthma	<p>Current Pharmaceutical Design, Vol. 2, No. 4, 1996, pp.413-428. P.425, left col., Chapter of asthma</p>
<p>Chronic obstructive pulmonary disease (COPD)</p> <p>Cough accompanied by asthma or chronic obstructive pulmonary disease (COPD)</p>	<p>Pharmacology & Therapeutics, Vol. 70, No. 1, pp. 39-63, 1996</p> <p>"This has led to the proposal that openers of BKCa channels could demonstrate therapeutic benefit in regulation of tone of the respiratory system"(P. 50, right col. L.1)</p> <p>British Journal of Pharmacology, (2003) 140 (5), pp. 939-947 (published on September 29, 2003)</p> <p>"Theophylline has been used worldwide for the treatment of asthma and chronic obstructive pulmonary diseases for several decades, due in part to its low cost and its ease of administration."(p.939 L.1)</p> <p>"We determine that the major mechanisms for theophylline-induced relaxation of the porcine tracheal smooth muscle include the <u>activation of BK channels</u> as well as the attenuation of Ca2+ sensitivity presumably through the actions of cAMP." (P. 946, right col. L.11)</p> <p>J. Clin. Invest., Vol. 99, No. 3, 1997, pp. 513-519</p> <p>"These data show that BKCa channel activation inhibits sensory nerve activity, resulting in a reduction of both afferent and efferent function. BKCa channel openers may therefore be of potential benefit in reducing neurogenic inflammation and central reflexes seen during inflammatory conditions of the airways, and may represent a new class of antitussive drug." (Abstract, L.17)</p>
Irritable bowel syndrome	<p>Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000.</p> <p>"Rapid synthesis of the BK channel opener CGS 7181 and its analogs." Bellef, Michel; Dube, Pascal; Dolman, Sarah; Scheigetz, John.</p> <p>"Calcium activated potassium (BK) channel openers are implicated in the excitability and the maintenance of the ionic homeostasis of the cells. They might be useful target for the treatment of disorders assocd. with <u>excessive neuronal discharge such as epilepsy, urinary incontinence and irritable bowel syndrome.</u>" (Abstract)</p>

	<p>Journal of Physiology (2000), 526.2, pp. 375-385 (Abstract) and</p> <p>"The sensory neurons within the gut wall are subjected to mechanical deformation of their processes and of their cell bodies. Deformation of the processes by stretch that occurs when the intestine is distended or the muscle contracts excites the neurons and triggers reflexes. Compression of the soma by pressure causes increased opening of potassium channels and thus has an inhibitory effect, which may be protective" (conclusion)</p>
Erectile dysfunction	<p>US 6,184,231 B1</p> <p>"The in vivo model on erectile function is described fully in the scientific literature [Rehman, J., Chenven, E., Brink, P., Peterson, B., Wolcott, B., Wen, Y. P., Melman, A., Christ, G.: Diminished neurogenic but not pharmacological erections in the 2- to 3-month experimentally diabetic F-344 rat. Am. J. Physiol. 272: H1960-H1971, (1997)]. Briefly, rats (250-600 g) were anesthetized using sodium pentobarbital, the abdomen opened and the cavernous nerve identified. A pressure catheter was placed in the right corpus cavernosum (crus) to measure intracavernous pressure (ICP). A second catheter was introduced into the carotid artery to measure blood pressure. Test compound (0.1, 0.3 and 1 mg/kg iV.) or vehicle (PEG 400) was given via a catheter placed into the jugular vein.</p> <p>Control intracavernous pressure responses were elicited by electrically stimulating the cavernous nerve via bipolar stimulating electrodes (20 Hz, 0.22 ms pulse width). Stimulus amplitude (0.2-20 mA) was adjusted to produce a submaximal intracavernous pressure response (typically 0.2 or 0.5 mA). A series of control intracavernous pressure responses were then obtained using a constant stimulus amplitude. Test compound or vehicle was then administered (200 μl i.v bolus) and the cavernous nerve was restimulated to evoke a cavernous pressure response at various times post-drug administration. Animals were excluded from the study if the initial ICP responses to nerve stimulation were unstable ("spiky" responses) or if there were time-dependent variations in the magnitude of the control responses. Animals were also excluded if the control ICP/BP response fell outside the 0.3-0.6 range. A repeated measures ANOVA was used for the evaluation of statistical significance.</p> <p>The compound of Example 20 (0.1-1 mg/kg) produced an augmentation of the ICP/BP responses elicited by sub-maximal stimulation of the cavernous nerve. A significant increase in the ICP/BP ratio was observed at doses from 0.1-1.0 mg/kg of compound tested." (Column 23 L. 48)</p>